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Award Number: W81XHW-05-1-0403

TITLE: Phase I/II Trial of Epothilone Analog BMS-247550, Mitoxantrone, and Prednisone in HRPC Patients Previously Treated with Chemotherapy

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14. ABSTRACT

his grant report includes a summary of the accomplishment of the statement of work, in addition to the complete protocol, consent, and Contracts and Grants office confirmation of submission of a grant to support the clinical trial. The clinical trial covered by this grant has been activated and is accruing patients.

15. SUBJECT TERMS
Prostate cancer, chemotherapy

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Grant #W81XHW-05-1-0403:
Department of Defense Clinical Trial Development Award Report

Summary of Work

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Assistant Clinical Professor
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This grant was awarded to support the development of "NCI 7347: Phase I/II trial of Epothilone Analog BMS-247550 (Ixabepilone), Mitoxantrone, and Prednisone in Hormone Refractory Prostate Cancer Patients Previously Treated with Chemotherapy."

Task 1

a. The phase I dose escalation schema:

For the phase I portion, the starting doses for BMS-247550 (ixabepilone) and mitoxantrone will be 20 mg/m^2 and 8mg/m^2, respectively, administered on day 1 of a 21 day cycle. Prednisone will be fixed at 5 mg PO BID. Subsequent doses are listed in the table below.

Cohort Dose Levels

		Mitoxantrone	BMS-247550 (ixabepilone)	Prednisone
Dose Level	I	8 mg/m^2	20 mg/m^2	5 mg PO BID
	II	8 mg/m^2	25 mg/m^2	5 mg PO BID
	III	10 mg/m^2	25 mg/m^2	5 mg PO BID
	IV	10 mg/m^2	30 mg/m^2	5 mg PO BID
	V	12 mg/m^2	30 mg/m^2	5 mg PO BID
	VI	12 mg/m^2	35 mg/m^2	5 mg PO BID

Drug	**Dose**	**Day**	**Schedule**
Mitoxantrone	See cohort dose levels	Day 1	Every 21 days
BMS-247550 (ixabepilone)	See cohort dose levels	Day 1	Every 21 days
Prednisone	5 mg PO BID	Day 1-21	Daily

b. Safety and monitoring plans, as well as the complete Data Safety and Monitoring Plan are included in the full protocol. (sections 8.0 and 9.0 pages 32-36)

Task 2:

a. Please see section 3.2 for eligibility criteria (protocol pages 6-9).
b. Please see section 4.0 for treatment plan (protocol pages 12-19).

c. Dose modification schema is contained in the treatment plan section 4.0.
d. The quality of life questionnaire was eliminated. The utility of a QOL instrument in a non-randomized phase II study with small numbers of patients is limited.
e. Please see sections 8.0 and 9.0 for the Data Safety and Monitoring Plan (pages 32-36)
f. As data management will be paperless for this clinical trial through the use of the clinical research database system, Velos, no forms were developed. However, data fields were written to ensure that all relevant data would be captured on the baseline patient characteristics, treatment-related side effects, adverse events, and anti-tumor responses.
g. See attached clinical trial protocol
h. All regulatory documents were submitted as required for IRB, CTEP, and FDA approval of this study by the regulatory affairs coordinator.
i,j,k,l All site committees, protocol review committees, and institutional review boards have reviewed and approved this trial. This clinical trial has been approved by the UCSF Comprehensive Cancer Center Institutional Review Board, the National Cancer Institute's Cancer Treatment Evaluation Program, the Food and Drug Administration, and is now open at UCSF.

The protocol and consent form follow this report.

This study will be conducted via the Department of Defense Prostate Cancer Clinical Trials Consortium. The participating centers include Oregon Health Sciences University, University of Michigan, and M.D. Anderson Cancer Center.

An R21 Quick Trials grant application entitled "Combination chemotherapy for taxane-refractory hormone refractory prostate cancer" has been submitted in response to the program announcement PAR-06-451 for the August 9th, 2006 deadline. Please see the letter from the UCSF Contracts and Grants office.

Reportable outcomes

This grant was intended to support the development of this clinical trial. The clinical trial will be reported for publication when it accrual has finished.

UCSF Urologic Oncology Clinical Research Program

NCI 7347: Phase I/II trial of Epothilone Analog BMS-247550 (Ixabepilone), Mitoxantrone, and Prednisone in Hormone Refractory Prostate Cancer Patients Previously Treated with Chemotherapy

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1.0 STUDY OBJECTIVES

1.1 Primary Objectives:

1.1.1 Phase I: To determine the MTD and dose-limiting toxicities of the combination of BMS-247550 (ixabepilone) and mitoxantrone/prednisone as chemotherapy for HRPC patients with disease progression after taxane-based chemotherapy.

1.1.2 Phase II: To assess the efficacy, as measured by reduction in PSA, of the combination of BMS-247550 (ixabepilone) and mitoxantrone/prednisone (MP) in hormone refractory metastatic prostate cancer patients who have received prior taxane-based chemotherapy.

1.2 Secondary Objectives:

1.2.1 To evaluate the overall safety and objective response rate of this regimen as second-line chemotherapy for patients with hormone refractory metastatic prostate cancer.

2.0 BACKGROUND

2.1 Current Treatment for Hormone Refractory Prostate Cancer

Prostate cancer is the second leading cause of cancer death in the United States.(1) Although most advanced prostate cancers are initially responsive to androgen ablation therapy, eventually all of these tumors become refractory to androgen deprivation.(2) As no curative option exists in metastatic HRPC, the goals of therapy in this setting have been, and continue to be, palliative.

Mitoxantrone in combination with a corticosteroid has been shown to have palliative activity in HRPC. Mitoxantrone's major toxicity is myelosuppresion; however, neutropenic fever is a rare occurrence.(3) Although related to the anthracyclines, mitoxantrone has significantly less cardiotoxicity than its relatives. Two randomized phase III trials have shown a clinical benefit to treatment with mitoxantrone and a corticosteroid compared with corticosteroid alone in patients with metastatic hormone refractory prostate cancer as first-line chemotherapy.(4, 5) Mitoxantrone, and prednisone has been shown to reduce pain and analgesic use, as well as provide objective and PSA responses in patients with HRPC (7% and 30-40%, respectively).(6, 7) Until relatively recently, mitoxantrone and prednisone has been the reference regimen for initial treatment of hormone refractory metastatic prostate cancer. It has been superseded in practice by taxane-based therapy as the standard of care in first line treatment.

Recently two large phase III studies demonstrated that docetaxel chemotherapy is associated with an improvement in median survival compared with mitoxantrone/prednisone (MP). In Tax 327, 1003 patients were randomized to weekly docetaxel/prednisone, every 3-week docetaxel/prednisone, or mitoxantrone/prednisone (MP).(8) Every 3-week docetaxel was associated with a 2.4-month median survival improvement compared with MP (18.9 vs. 16.5 months, p=0.009). In SWOG 9916, 620 patients were randomized to either every 3-week docetaxel/ estramustine or MP; the docetaxel arm was associated with a 2-month survival advantage relative to MP (18 vs. 16 months). (9)

2.2 Second-line chemotherapy for HRPC

Despite these advances, most patients eventually progress through taxane-based treatment. Many of these patients are reasonably healthy and wish additional treatment. Currently, there is no standard chemotherapy regimen for second-line treatment of patients with hormone refractory prostate cancer after progression on taxane-based therapies. The community de-facto standard of care has been MP, in the absence of any data on its activity in this setting. Novel therapeutics as well as combinations of existing drugs must be investigated in this patient population. If these drugs and combinations have activity in the second-line setting, they may ultimately be tested in the first-line setting to improve first-line chemotherapy.

2.3 BMS-247550 (ixabepilone)

The epothilones are a new class of non-taxane tubulin polymerization agents obtained by fermentation of the myxobacteria *Sorangium cellulosum*.(10) The chief components of the fermentation process are epothilones A and B. In 1994, the National Cancer Institute discovered that the epothilones possess potent cytotoxic activity. This cytotoxic activity, like those of the taxanes, has been linked to stabilization of microtubules that results in mitotic arrest at the G2/M transition.(11) Significantly, in cell culture, the epothilones are active against various paclitaxel resistant cell lines, encompassing both the multidrug resistance (MDR) and tubulin mutation modes of resistance.

BMS-247550 (ixabepilone) is a semi-synthetic analog of the natural product epothilone B specifically designed to overcome the metabolic instability of the natural product. Similar to paclitaxel, BMS-247550 (ixabepilone) blocks cells in the mitotic phase of the cell division cycle and is a highly potent cytotoxic agent capable of killing cancer cells at low nanomolar concentration. Most importantly, BMS-247550 (ixabepilone) has demonstrated impressive antitumor activity in a number of preclinical human tumor models, including cancer cells that are naturally insensitive to taxanes or have developed resistance to taxanes through mutation, as well as in taxane-sensitive tumor models.

2.3.1 BMS-247550 (ixabepilone) in HRPC

BMS-247550 (ixabepilone) has been shown to have anti-tumor activity in patients with metastatic HRPC. A multi-institutional phase II study evaluating BMS-247550 (ixabepilone) with and without estramustine phosphate (EMP) as first-line chemotherapy for HRPC demonstrated PSA response proportions of 69% and 48%, respectively.(12) Objective responses were observed in 48% and 32% of patients with measurable disease. Grade 3-4 neuropathy was observed in 7% of patients treated with BMS-247550 (ixabepilone) + EMP and 13% of patients treated with BMS-247550 (ixabepilone) alone. Rates of febrile neutropenia in this trial were 9%with BMS-247550 (ixabepilone)/EMP and only 4% with BMS-247550 (ixabepilone) alone. In general, BMS-247550 (ixabepilone) treatment was well tolerated.

BMS-247550 (ixabepilone) (35 mg/m^2 IV q21 days) is being tested in a multicenter randomized phase II study of mitoxantrone and prednisone or BMS-247550 (ixabepilone) as second-line therapy in patients with taxane resistant disease (NCI #6046). Preliminary results indicate the BMS-247550 (ixabepilone) is tolerable as second-line chemotherapy, with modest hematologic toxicity being most prominent (primarily neutropenia: BMS-247550 (ixabepilone): 39% grade 3/4). One patient (out of 40) treated with BMS-274550 (ixabepilone) died of neutropenic sepsis, while two others (5%) experienced grade 3 febrile neutropenia. Treatment with BMS-247550 (ixabepilone) as second-line therapy was associated with only one grade 3 neuropathy (out of 40 patients treated as second-

and third-line therapy). In preliminary results, BMS-247550 (ixabepilone) is associated with a 20% 2nd-line response proportion (4/24) In addition, during this study, patients receiving crossover 3rd-line therapy after progression on mitoxantrone/prednisone have demonstrated PSA responses to BMS-247550 (ixabepilone) (2 patients). This study is expected to close in July 2005.

2.4 Rationale

Currently, patients with hormone refractory prostate cancer have very limited options for treatment after progression on first-line chemotherapy. Many of these patients remain quite healthy and desire further treatment. Randomized phase III data have shown that docetaxel-prednisone is superior to mitoxantrone/prednisone (MP) as first line chemotherapy for HRPC. However, the median duration of response to docetaxel remains only 6-9 months. Treatment for patients who have disease progression after taxane-based chemotherapy has not been defined. In the community, MP is the de-facto standard second-line regimen in patients who have received prior taxane-based chemotherapy. BMS-247550 (ixabepilone) is an experimental novel agent that demonstrates pre-clinical evidence of activity in taxane-resistant cancers, and has demonstrated substantial activity against HRPC in the first-line setting.(12) MP is a well-tolerated regimen, making it an ideal regimen for the second-line treatment of these heavily pre-treated patients.

We are testing BMS-247550 (ixabepilone) (35 mg/m^2 IV q21 days) vs. mitoxantrone (14 mg/m^2 IV q21 days)/prednisone individually in a randomized multicenter phase II study as second-line therapy in patients with taxane resistant disease (NCI #6046). Patients on this study are randomized to either MP or BMS-247550 (ixabepilone), with the option of crossover to the other arm for progression or excessive toxicity. Preliminary results of this study indicate the individual treatments have been tolerable, with hematologic toxicity being most prominent. Overall, neutropenic fever was observed in less than 10% of patients in all arms of the trial, although grade 3-4 neutropenia was observed in approximately 40% of patients on study. Other toxicities have been largely non-overlapping between the two regimens (see Appendix 2).

Responses have been observed with both MP and BMS-247550 (ixabepilone) in the second-line setting. In preliminary results, BMS-247550 (ixabepilone) is associated with a 20% 2nd-line response proportion, and MP is associated with a 15% 2nd-line PSA response proportion. In addition, during this study, patients receiving crossover third-line therapy after second-line progression have demonstrated third-line PSA responses to both BMS-247550 (ixabepilone) and mitoxantrone. As a result, both drugs appear to have at least modest activity after the first-line setting, and at least partial clinical non-cross resistance. Therefore, based on the activity seen with each drug separately, the lack of complete cross-resistance, the modest toxicity profile of each agent individually, and potential additive effects, we plan to test these agents together as second-line combination therapy for HRPC.

In this previous study, we asked the clinical question of whether either BMS-247550 (ixabepilone) or mitoxantrone has activity against taxane resistant prostate cancer. To do this, we required that patients treated with taxane-based chemotherapy progress during chemotherapy or within 60 days of stopping chemotherapy. However, in practice, this is a very small patient population, and these restrictive eligibility requirements resulted in slow accrual. Therefore, in this successor study, we are expanding enrollment to any patient with disease progression (PSA progression, bone scan progression, or RECIST progression) during taxane-based chemotherapy or after cessation of taxane-based chemotherapy. We anticipate this change will increase accrual, and will make the results of this study more broadly applicable to prostate cancer patients, many

of whom stop chemotherapy without strict evidence of disease progression (either for toxicity or patient preference).

The phase I portion of this study will determine the maximum tolerated doses of these drugs in combination. The MTD in phase I studies of BMS-247550 (ixabepilone) in HRPC was 35 mg/m^2 every three weeks. The starting doses of BMS-247550 (ixabepilone) and mitoxantrone have been empirically selected to be 20 mg/m^2 and 8 mg/m^2, respectively. BMS-247550 (ixabepilone) will be escalated by 5 mg/m^2 increments on alternate dose levels to 35 mg/m^2, the dose used in NCI #6046. Mitoxantrone will be escalated by 2 mg/m^2 increments on alternate dose levels to 12 mg/m^2, the dose used in the Canadian Phase III study in HRPC.(5) We have chosen 12 mg/m^2 as the maximum possible mitoxantrone dose in this study due to myelosuppresion seen at 14 mg/m^2 in our single agent second-line study. If a dose limiting toxicity is seen in dose level I, there will be no dose de-escalation and the study will be terminated.

The phase II portion of this study will evaluate the PSA response proportion of BMS-247550 (ixabepilone), mitoxantrone, and prednisone at the MTD to identify a potentially active regimen for 2nd-line treatment of HRPC. Based on the PSA response proportion of NCI6046, a response proportion of 35%, compared to a null hypothesis of 20%, would provide clinically meaningful evidence of at least additive activity of mitoxantrone and BMS-247550 (ixabepilone). Therefore, the phase II portion of this study will enroll 58 patients. While a $\geq$ 50% decline in PSA is not a surrogate for survival, the use of PSA declines is generally accepted as a screen for activity in Phase II trials using cytotoxic agents.(13). The Consensus Criteria will be used to evaluate post-therapy PSA changes in this trial.

3.0 STUDY DESIGN

3.1 General Study Design

This study is a multi-center phase I/II trial of BMS-247550 (ixabepilone), mitoxantrone, and prednisone in HRPC patients previously treated with taxane-based chemotherapy. The phase I portion of this trial will establish the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) for the combination of BMS-247550 (ixabepilone), mitoxantrone and prednisone. If two DLT's occur at the initial dose level, there will be no dose de-escalation and the study will be closed. The phase II portion of the study will use the MTD of the combination of BMS-247550 (ixabepilone), mitoxantrone, and prednisone as defined in the phase I portion to determine the activity of the regimen by PSA response proportion.

3.2 Eligibility Criteria

1. Histologically confirmed adenocarcinoma of the prostate.

2. Progressive metastatic prostate cancer (positive bone scan or measurable disease) despite castrate levels of testosterone (either from orchiectomy or LHRH agonist therapy).

3. Patients may have either <u>non-measurable disease</u> OR <u>measurable disease</u>

4. All patients must have a PSA $\geq$ 5 ng/mL.

5. Progressive disease based on any one of the following:
    1) transaxial imaging
    2) a rise in PSA

3) radionuclide bone scan.

Patients whose sole manifestation of progression is an increase in disease-related symptoms are not eligible.

a. For patients with measurable disease, progression will be defined by the RECIST criteria.(14)

b. For patients with no measurable disease, a positive bone scan and elevated PSA will be required. PSA evidence for progressive prostate cancer during or after first-line chemotherapy consists of a PSA level of at least 5 ng/ml which has risen on at least 2 successive occasions, at least two weeks apart. If the confirmatory PSA (#3) value is less (i.e., #3b) than the screening PSA (#2) value, then an additional test for rising PSA (#4) will be required to document progression.

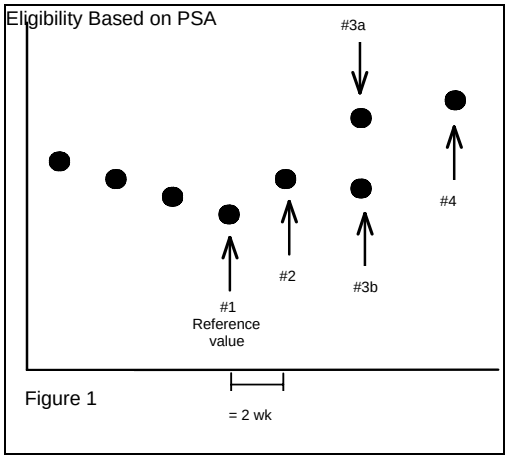

Figure 1

c. Radionuclide bone scan: new metastatic lesions

6. Patients must have received at least three cycles of paclitaxel- or docetaxel-based therapy, with disease progression documented during therapy or following cessation of therapy. Patients may not have received more than one prior chemotherapy regimen.
   a. Patients who required changes in their prior chemotherapy regimen (addition of other agents) for disease progression will be considered to have had two prior chemotherapy regimens and are not eligible.
   b. Patients who have been re-treated with the same taxane-based regimen are considered eligible provided other eligibility criteria are met.
   c. Patients will be excluded if they have previously received mitoxantrone, BMS-247550 (ixabepilone), or other epothilones.

7. Testosterone < 50 ng/dL. Patients must continue primary androgen deprivation with an LHRH analogue if they have not undergone orchiectomy.

8. CTC (ECOG) Performance Status 0 –2 (see Appendix 1).

9. Required Laboratory values:
   a. Creatinine $\leq$ 1.5 x upper limits of normal (ULN). If Cr. > 1.5 x ULN, then calculated creatinine clearance > 40cc/min.
   b. ALT and AST < 2.5 x ULN
   c. Granulocytes $\geq$ 2,000/mm^3
   d. Platelets $\geq$ 100,000/ mm^3
   e. Total bilirubin < 1.5 x ULN

10. Ejection fraction by MUGA scan or echocardiogram $\geq$ lower limit of institutional normal. Patients with significant cardiovascular disease including congestive heart failure (NYHA class III or IV), active angina pectoris or recent (within 6 months) myocardial infarction are excluded.

11. Patients receiving hormonal therapy (i.e. any dose of megestrol acetate (Megace), Proscar (finasteride), any herbal product known to decrease PSA levels (e.g., Saw Palmetto and PC-SPES)) other than LHRH agonist or a stable dose of corticosteroid from a prior chemotherapy regimen must discontinue the agent for at least 4 weeks prior to enrollment. Progressive disease (as defined in section 6.3) must be documented after discontinuation of the hormonal therapy.

12. No other systemic therapies for prostate cancer within 28 days prior to initiation of this protocol.

13. Prior radiation therapy completed $\geq$ 4 weeks prior to enrollment.

14. No radiopharmaceuticals (strontium, samarium) within 8 weeks prior to enrollment.

15. Patients with serious intercurrent infections, or nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this therapy are not eligible.

16. Patients with psychiatric illness/social situations that would limit compliance with study requirements are not eligible.

17. Patients with pre-existing neuropathy greater than CTC Grade 1 (motor or sensory) are excluded.

18. Patients with known prior severe hypersensitivity reactions to agents containing Cremophor®EL are excluded.

19. Patients with known active brain metastases are excluded because of their poor prognosis and because neurologic dysfunction would confound evaluation of neurologic toxicity from treatment are excluded. Head CT is **NOT** routinely required prior to enrollment.

20. Patients with a "currently active" second malignancy other than non-melanoma skin cancer are excluded. Patients are not considered to have a "currently active"

malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse.

21. Patients must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry, for the duration of study participation and for 3 months after discontinuing therapy. Should a patient's sexual partner become pregnant or suspect she is pregnant while the patient is participating in this study, he should inform the treating physician immediately.

22. Life expectancy $\geq$ 12 weeks.

23. Concurrent use of moderate to strong CYP3A4 inhibitors is not allowed (see Section 5.1.8).

24. Inclusion of Minorities: Men and members of all ethnic groups are eligible for this trial. The proposed study population is illustrated in the table below (for the phase II portion of this trial), based on current accrual patterns:

	Race/Ethnicity					
Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male	39	6	0	3	0	58
Female	0	0	0	0	0	0
Total	39	6	0	3	0	58

3.3 Subject Recruitment & Study Sites

Patients will be screened for interest and eligibility by the medical oncologists in the Urologic Oncology Practice at UCSF Comprehensive Cancer, UCSF-Veterans Affairs Medical Center, Oregon Health Sciences University (OHSU) Cancer Institute, MD Anderson Cancer Center, and University of Michigan Comprehensive Cancer Center. Patients to be screened will include those currently followed in these practices, as well as those referred from outside providers.

3.4 Registration Procedures

A centralized, 3-part registration procedure will be used. After eligibility screening, patients selected to participate will be registered with their study site/institution first, then with the lead center and finally in the consortium database (Velos eResearch).

Institutional Registration

Patient registration at each study site/institution will be conducted according to the institution's established policies. Prior to registration, patients will be asked to sign and date an Institutional Review Board (IRB)-approved consent form and a research authorization form/Heath Insurance Portability and Accountability Act (HIPAA) authorization form. Patients must be registered with both the institution and the sponsor before beginning any treatment or study activities.

Lead Center Registration

To initiate lead center registration, study sites/institutions should forward copies of the signed informed consent, research authorization/HIPAA forms, the institutional registration form, plus any required laboratory tests, to the lead center by fax. Upon receipt of these forms, the lead center will confirm patient eligibility with study personnel, assign a unique patient study identification number, and complete patient registration.

Prior to the initiation of protocol therapy, patients must be registered with the UCSF Urologic Oncology Clinical Research Coordinator. Patients may be registered Monday – Friday between 9:00 AM and 5:00 PM PST. To register a patient, please fax the Enrollment Form along with a copy of the signed informed consent signature page, and the completed eligibility checklist to (415) 353-9566. Please call when faxing enrollment information to verify receipt and expedite processing.

A patient cannot be treated until the Enrollment Form is faxed back.

Consortium Registration

Once registration has been completed at the patient's institution and with the Lead Center, the patient will be registered in the centralized database for the consortium (Velos eResearch). Registration procedures will be detailed in the *PCCTC Velos eResearch Data Entry Manual*.

3.5 PRETREATMENT EVALUATION (see chart in section 3.6)

3.5.1 Clinical (within 14 days prior to initiating treatment)

a. Complete history and physical examination, including height, weight, and baseline evaluation of symptoms, pain and medications
b. Performance Status (ECOG scale)
c. Informed Consent

3.5.2 Laboratory (within 14 days prior to initiating treatment)

a. Complete blood count including differential and platelet count
b. Alkaline phosphatase, albumin, total bilirubin, BUN, calcium, creatinine, glucose, LDH, SGOT, SGPT, electrolytes, magnesium
c. PSA
d. Testosterone level (may be obtained within 28 days prior to protocol registration)

3.5.3 Radiographic and Diagnostic Studies (within 28 days of initiating treatment)

a. Radionuclide bone scan
b. CT scan of the chest, abdomen, and pelvis (MRI acceptable)
c. MUGA or echocardiogram (may be performed within 42 days of initiating treatment)

3.6 Required Studies

Studies will be performed as noted in the table below:

		Study Treatment Repeat cycle every 21 days*			
STUDY	**PRE-RX[1]**	**Day 1**	**Days 8 and15[7]**	**Every 3 cycles**	**Off Study**
Physical exam, PS, AE/Toxicity eval	X	X			X[2]
CBC, diff, plts,	X	X	X		X[2]
Glucose, Electrolytes, magnesium, Alk phos, LDH, albumin, calcium, SGOT, SGPT, Tbili, BUN, Cr, PSA	X	X			X[2]
Testosterone	X				
CT or MRI chest/abd/pelvis	X			X[3]	X[4]
Bone Scan	X			X[3]	X[4]
Ejection fraction by MUGA or echocardiogram	X[5]			X[5]	
Serum/Plasma/Urine banking[6]	X			X	X

[1] All pretreatment procedures and tests, excluding bone and CT scans, MUGA/echocardiogram, chest imaging, and testosterone level, must be done within 14 days prior to initiating study treatment. Bone scan, CT scan, and testosterone level may be done within 28 days of initiating study treatment. Ejection fraction by MUGA or echo may be obtained within 42 days of initiating study treatment.

[2] Does not need to be repeated if done within the previous 14 days.

[3] Repeat if positive at pre-treatment or as clinically indicated.

[4] Does not need to be repeated if done within the previous 28 days.

[5] MUGA or echocardiogram will be done at baseline on all patients, and then repeated every 3 cycles thereafter, or as clinically indicated (see Section 4.3.2.8)

[6] Serum, Plasma and Urine Banking is optional and patients will initial a separate statement in the informed consent

[7] Day 8 and Day 15 labs have a +/- 24 hour window

*For cycle 1, pre-treatment labs may be used as day 1 labs. For subsequent cycles, labs may be obtained up to 48 hours prior to day 1 of treatment.

3.7 Serum, Plasma and Urine Banking

At each time point indicated in section 3.6, 20cc of whole blood will be collected in one tigertop tube (serum) and one lavender top tube (plasma) and centrifuged at 3000 rpm for 10 minutes. The serum and plasma will be decanted into two polypropylene screw cap (leak-proof) vials (four total vials) that have been properly labeled with the unique patient identifier provided at registration and stored at –80°C.

At each time point, urine will be collected in a single 50cc polypropylene screw-cap container (preferably plastic test tube) which has been properly labeled, frozen and stored at -20° C until shipping. The UCSF Comprehensive Cancer Center Tissue Bank will serve as a repository for banking human samples. Specimen and data registries will be kept by the Cancer Center. This

registry will have a coordinated database to protect patient confidentiality and safety. The samples will receive a patient-insensitive identifier and the link to patient identity will be kept in a locked file with access only by the director of the Tissue Bank. Other investigators will have access to the samples only through established Tissue Core procedures. That is, investigators must submit a written request to use the stored samples as part of a CHR-approved protocol that is reviewed by the Tissue Core committee. This review limits the testing that can be done on these samples. No information about germline genetic mutations will be done on these samples. Patients have the right at any time to request that all remaining samples be destroyed. The patient or relatives may be contacted about future, additional research on stored samples, if necessary. Additional written consent will be required if additional samples are to be taken.

4.0 TREATMENT PLAN

This trial will have two phases. The first, a phase I dose-finding study will determine the MTD and DLTs of the combination of BMS-247550 (ixabepilone), mitoxantrone, and prednisone. The second, phase II portion will evaluate the activity of these three medications at the MTD determined in the phase I portion.

Two separate dose guidelines will be used in this trial:

a. Cohort dose level in the phase I portion of the study only (referred to by Roman numerals: I, II, III, etc).
b. Individual patient dose level: individual patients may have their doses modified (reduced) for toxicity in both the phase I and phase II portions of the study (referred to by Arabic numerals: 0, -1, -2).

4.1 For both phases of this trial:

1. Each cycle is 21 days long.

2. Patients may receive full supportive care including erythropoetin, transfusions of blood and blood products, bisphosphonates, antibiotics, and anti-emetics. The American Society of Clinical Oncology (ASCO) guidelines for the use of colony-stimulating factors (CSFs) will be followed.(15) The use of CSFs such as G-CSF and GM-CSF for the treatment of febrile neutropenia is at the discretion of the treating physician. While routine use in this circumstance is discouraged, CSF use as an adjunct to appropriate antibiotic therapy may be indicated in certain patients. The primary prophylactic use of CSFs to avoid myelosuppresion is prohibited. Radiation therapy may not be administered and the need for such would indicate progressive disease requiring the patient be removed from study.

3. All patients will be premedicated to prevent a hypersensitivity reaction related to BMS-247550 (ixabepilone) as follows:
   Premedicate one hour prior to the infusion of BMS-247550 (ixabepilone) with:
   a) Oral H1 blocker (diphenhydramine 50 mg), and
   b) Oral H2 blocker (nizatidine 150 mg or famotidine 40 mg).
   Histamine is a major mediator of anaphylactic/ anaphylactoid responses in man, such as those induced by Cremophor®EL. Both H1 and H2 blockers are included because blockade of both classes of receptors has been shown to block cardiovascular effects of histamine to a greater extent than either blocker alone. Note that, in the event of patient intolerability to the antihistamines listed above, alternatives may be substituted at the Investigator's discretion. In addition, if the specified antihistamine or corticosteroid is not available, an equivalent antihistamine or corticosteroid may be substituted.

4. Mitoxantrone will be administered intravenously on day 1 of each cycle, prior to BMS-247550 (ixabepilone). Mitoxantrone may be administered either via a central or peripheral intravenous line in a short infusion (30 minutes). The incidence of congestive heart failure increases significantly after 140 mg/m^2 cumulative dose. Physicians may use their discretion to continue treatment beyond this cumulative dose with close monitoring of cardiac function.

5. BMS-247550 (ixabepilone) should be administered as a continuous infusion over three hours on day 1 of each cycle. See Section 5.1.2 for details on preparation of BMS-247550 (ixabepilone) for intravenous administration. After confirming that the required volume has been administered, solution remaining in the line and container should be disposed of per institution policies for cytotoxic disposal. The patient's blood pressure and heart rate should be measured at baseline and every 15 minutes during the first hour of BMS-247550 (ixabepilone) infusion for cycles 1 through 4. Since BMS-247550 (ixabepilone) is formulated in polyoxyethylated castor oil (Cremophor®EL), hypersensitivity reactions may occur. Therefore, patients should be monitored closely for any signs or symptoms of hypersensitivity and emergency equipment must be available to treat possible anaphylactic/ anaphylactoid reactions as outlined in number 8 below.

6. Prednisone dose will be 5 mg by mouth twice a day, continuously. At the conclusion of treatment, prednisone will be tapered over two weeks.

7. Patients will be allowed to receive at least 3 cycles of treatment before discontinuation of treatment for progressive disease at the physician's discretion.

8. **Treatment of Hypersensitivity Reactions**
   In case of hypersensitivity reactions, the Investigator should institute treatment measures deemed medically appropriate. Based on prior experience with paclitaxel, the following treatment recommendations may be applicable:

CTC Grade 1 Allergic Reaction/Hypersensitivity (transient rash, drug fever < 38°C):
- Supervise at the bedside without further treatment.

CTC Grade 2 Allergic Reaction/Hypersensitivity (urticaria, drug fever ≥ 38°C):
- Interrupt the infusion of BMS-247550 (ixabepilone),
- After recovery of symptoms, resume the infusion at a slower rate and if no further symptoms appear, complete the administration of the dose. (Note: It is recommended that the infusion of BMS-247550 (ixabepilone) be completed within 6 hours of the final dilution. See Section 5.1.2).

Recurrent CTC Grade 2 or CTC Grade 3 or 4 Allergic/Hypersensitivity Reactions:
Stop the infusion.
Administer additional doses of H1 and H2 blockers intravenously. Administer IV steroids (see discussion below) and consider epinephrine and bronchlodilators as clinically indicated.
Further treatment should be delayed 24 hours.

Prior to rechallenge and with all subsequent cycles, give both an H1 and H2 blocker intravenously plus dexamethasone 20 mg x 2 doses (orally or intravenously) 12 and 6 hours pre BMS247550 (ixabepilone).

Dexamethasone could be used at the investigator's discretion in subsequent cycles for recurrent (i.e. occurring despite slowing infusion as discussed above) grade 2 reactions but would not be mandated. Note that the administration of dexamethasone immediately prior to BMS247550 (ixabepilone) is unlikely to be effective.

9. When calculating body surface areas, actual heights and weights should be used. There should be no adjustment to "ideal" weight. The total dose delivered should be rounded to the nearest mg.

4.2 Phase I dose escalation study

This is an open label study of BMS-247550 (ixabepilone) (20-35mg/m2 IV q21 days) in combination with mitoxantrone (8-12 mg/m2 IV q21 days) and prednisone 5mg orally BID. Up to six cohorts will be enrolled to determine the MTD and DLT of this combination.

a. For the phase I portion, the starting doses for BMS-247550 (ixabepilone) and mitoxantrone will be 20 mg/m^2 and 8mg/m^2, respectively, administered on day 1 of a 21 day cycle. Prednisone will be fixed at 5 mg PO BID. Subsequent doses are listed in the table below.

Cohort Dose Levels

		Mitoxantrone	BMS-247550 (ixabepilone)	Prednisone
Dose Level	I	8 mg/m^2	20 mg/m^2	5 mg PO BID
	II	8 mg/m^2	25 mg/m^2	5 mg PO BID
	III	10 mg/m^2	25 mg/m^2	5 mg PO BID
	IV	10 mg/m^2	30 mg/m^2	5 mg PO BID
	V	12 mg/m^2	30 mg/m^2	5 mg PO BID
	VI	12 mg/m^2	35 mg/m^2	5 mg PO BID

Drug	**Dose**	**Day**	**Schedule**
Mitoxantrone	See cohort dose levels	Day 1	Every 21 days
BMS-247550 (ixabepilone)	See cohort dose levels	Day 1	Every 21 days
Prednisone	5 mg PO BID	Day 1-21	Daily

4.2.1 Dose limiting toxicity

For the purposes of Phase I dose escalation, a DLT will be defined as:

1. Toxicity occurring within the first 21 days of therapy
2. ≥ Grade 3 non-hematologic toxicity, excluding fatigue, alopecia, or toxicity attributed to androgen deprivation
3. Hematologic toxicity defined as:
   - Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding

- Grade 4 neutropenia which persists for >7 days
- Grade 4 neutropenia associated with fever >38.5C
- Excludes lymphopenia or anemia of any grade

4. Removal of a patient from therapy due to toxicity attributable to treatment

If neuropathy is identified as the DLT in dose levels II-VI (specific to BMS-247550 [ixabepilone]), then the previous dose level of BMS-247550 (ixabepilone) will be named the MTD for BMS-247550 (ixabepilone). Mitoxantrone will then be escalated by 2mg/m^2 in successive dose levels until an MTD or a dose of 12 mg/m^2 is reached.

4.2.2 Phase I: Rules for dose escalation and de-escalation

Beginning with the starting dose level, three patients will be treated at each dose level. Three patients must complete at least 1 cycle of therapy prior to the accrual of the next cohort of 3 patients at the higher dose level. A minimum of 3 patients and a maximum of 36 patients will be treated in the phase I portion of the study.

4.2.2.1 Dose escalation rules

Mitoxantrone and BMS-247550 (ixabepilone) will be escalated according to the rules outlined below.

1. If 0 of 3 patients in a cohort experience dose limiting toxicities, then the next cohort of 3 patients will be treated at the next higher dose level.
2. If 1 of 3 patients in a cohort experiences a DLT then the cohort will be expanded to treat an additional three patients. If only one of 6 patients experiences a DLT, then the next cohort of patients will be treated at the next higher dose level.
3. If two or more patients in a cohort experience a DLT, then the MTD has been exceeded. The previous dose level will be considered the MTD. If only 3 patients were treated at the previous dose level, an additional three patients will be treated at that dose level to confirm the MTD.
4. If more than 1 of 3 or 1 of 6 patients experience a DLT at dose level I then the study will be terminated, as the MTD cannot be determined and de-escalation is not planned.
5. If the doses of both drugs are escalated to dose level VI with 0 of 3 or 1 out of 6 patients experiencing a DLT, then this will be considered the MTD.
6. Patients treated on the phase I study who remain on therapy after the determination of the recommended phase II dose (RP2D) may have their dose escalated to the RP2D after discussion with their treating physician. These patients will be included in the safety analysis but not the phase II response analysis.

4.2.2.2 Dose modification due to prednisone toxicity

Corticosteroid toxicity such as hyperglycemia, insomnia, hypertension, gastritis/ulcers, and mental status/mood changes may occur even with the doses of prednisone used in this study. Treating physicians may modify the doses of prednisone as clinically indicated. Cessation of prednisone therapy is not a reason to remove a patient from protocol therapy or to be considered a DLT.

4.3 Phase II

Once the MTD has been determined, then the phase II portion of this study will begin. The doses used will be at the MTD from the phase I portion of this study. A total of 58 patients will be treated on at the MTD.

4.3.1 Individual patient dose modification guidelines

- Dose modifications are made according to the system showing the greatest degree of toxicity
- Toxicity will be graded using the NCI Common Toxicity Criteria Version 3.0.
- If toxicity occurs, the appropriate treatment will be instituted to ameliorate signs and symptoms including anti-emetics for nausea and vomiting, anti-diarrheals for diarrhea, and anti-pyretics and antihistamines for drug fever before toxicity grade is determined.
- The following guidelines (section 4.2.2) will be utilized to modify doses in response to toxicity in individual patients in both the phase I and II portions of the study.
- Once a dose has been reduced for toxicity, it will not be re-escalated.
- If a given agent requires dose reduction more than twice, then that agent will be discontinued, but does not require removing the patient from protocol therapy.
- If toxicity occurs mandating two dose reductions for both agents, the patient will be removed from therapy and followed for progression and survival.

4.3.2 Dose Modifications

4.3.2.1 Dose modifications for toxicity attributable to both BMS-247550 (ixabepilone) and mitoxantrone

The possible dose levels for individual patients are:

Dose Level	BMS-247550 (ixabepilone) Dose	Mitoxantrone Dose
0	**MTD or phase I assigned dose**	**MTD or phase I assigned dose**
-1	**MTD or phase I assigned dose -5 mg/m^2**	**MTD or phase I assigned dose -2 mg/m^2**
-2	**MTD or phase I assigned dose -10 mg/m^2**	**MTD or phase I assigned dose -4 mg/m^2**

4.3.2.2 For toxicities $\geq$ grade 3 (except for alopecia, lymphocytopenia or anemia, toxicities related to androgen deprivation, and as outlined below), both drugs should be withheld until resolution to $\leq$ grade 1 (or to baseline if baseline was greater than grade 1), then reinstituted, if medically appropriate at dose level –1 or at the discretion of the study chair. Recurrence of (same or different) toxicities $\geq$ grade 3 will require similar dose reduction process, with reinstitution of therapy at dose level -2.

4.3.2.3 The patient will be removed from treatment if:

a. There is a delay of treatment $\geq$ 3 weeks for recovery from toxicity to permissible level
b. There is recurrence of $\geq$ grade 3 toxicities despite de-escalation to dose-level – 2

4.3.2.4 Dose modification due to prednisone toxicity

Corticosteroid toxicity such as hyperglycemia, insomnia, hypertension, gastritis/ulcers, and mental status/mood changes may occur even with the doses of prednisone used in this study. Treating physicians may modify the doses of prednisone as clinically indicated. Cessation of prednisone therapy is not a reason to remove a patient from protocol therapy.

4.3.2.5 Dose modification due to neurotoxicity (attributable to BMS-247550 [ixabepilone])

Specific instructions for dose modification for neurotoxicity:

Toxicity	**Dose adjustment**
Grade 0, 1	No action
Grade 2 or Grade 3	Hold until ≤ grade 1 All subsequent cycles at dose level –1A
Recurrent Grade 3 or Any Grade 4	Discontinue BMS-247550 (ixabepilone)
Recurrent Grade 2	Hold until ≤ grade 1 All subsequent cycles at dose level -2A
Recurrent ≥ Grade 2 at dose level –2A	Discontinue BMS-247550 (ixabepilone)

Dose Reductions based on neurotoxicity:

Dose Level	**BMS-247550 (ixabepilone) Dose**	**Mitoxantrone Dose**
0	**MTD or phase I assigned dose**	**MTD or phase I assigned dose**
-1A	**MTD or phase I assigned dose -5 mg/m^2**	**MTD or phase I assigned dose**
-2A	**MTD or phase I assigned dose -10 mg/m^2**	**MTD or phase I assigned dose**

4.3.2.6 Hematologic Toxicity

4.3.2.6.1 Dose Adjustment Based on Nadir Counts

a. Grade 1, 2 and 3 leukopenia, neutropenia, or thrombocytopenia without bleeding and uncomplicated grade 4 leukopenia or neutropenia does not require dose modification. Anemia and lymphopenia of any grade do not require dose modification.

b. Grade 4 neutropenia associated with a fever (≥ 38.5°C) or grade 4 neutropenia that persists > 7 days will result in dose reduction to level -1. Recurrence at dose level -1 will result in dose reduction to level -2. Recurrence at dose level -2 will result in removal from treatment.

c. Grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding will result in dose reduction to level -1. Recurrence of the same toxicity at dose level –1 will result in reduction to dose level -2. Recurrence at dose level -2 will result in removal from treatment.

4.3.2.6.2 Dose Adjustment Based on Day 1 ANC and Platelet Count for Each Cycle

a. For ANC ≥ 1,500 and Plt ≥ 75,000:
100% BMS-247550 (ixabepilone), 100% Mitoxantrone

b. For ANC < 1,500 or Plt < 75,000:
Hold therapy, repeat CBC weekly, and retreat at dose level -1 once ANC > 1,500, and Plt ≥ 100K. Recurrence at dose level -1 will result in dose reduction to level -2. Recurrence at dose level -2 will result in removal from treatment.

4.3.2.6.3 The patient will be removed from treatment if there is recurrence of hematologic toxicity requiring dose adjustment despite de-escalation to dose-level – 2

4.3.2.7 Hepatic Toxicity

Patients who develop abnormal liver function tests, as defined below, for any reason while on study will have treatment held and/or reduced according to the following schedule:

Dose Modifications for Abnormal Liver Function

Bili		Alk Phos *		SGOT	Action
grade 1	or	≥ grade 3	or	≥ grade 3	Hold both drugs until bili grade 0 AND alk phos ≤ grade 1 AND SGOT < grade 1, then resume treatment for next and all subsequent cycles at dose level –1. Recurrence at dose level –1 will result in reduction to dose level –2. Recurrence at dose level –2 or the need to hold Rx for >3 weeks will require removal from treatment.

* Elevated alkaline phosphatase that can be attributed to bone metastases does not require dose adjustment.

4.3.2.8 Cardiovascular

EKG changes, arrhythmias, tachycardia, and/or chest pain should be managed based on the specific findings. All patients will undergo baseline ejection fraction determination by MUGA, and this evaluation will be repeated for patients receiving mitoxantrone/prednisone after the first 3 cycles, then every 3 cycles thereafter, and as clinically indicated. If ejection fraction decreases to below institutional limits, or declines by an absolute level of ≥ 15%, mitoxantrone will be discontinued. This does not mandate that the patient be removed from protocol treatment if the patient is receiving BMS-247550 (ixabepilone) with acceptable non-cardiovascular toxicity. Clinicians must exercise their discretion in treating patients with mitoxantrone beyond a cumulative dose of 140mg/m^2.

4.3.2.9 Hypersensitivity

No dose reductions should be made. Acute hypersensitivity reactions to BMS-247550 (ixabepilone) should be managed according to section 4.1.

4.4 Cycle Delays

Initiation of subsequent cycles may be delayed for a maximum of three weeks for toxicity or at the discretion of the treating physician. Any patient who fails to recover from a treatment related toxicity to baseline or Grade 1 within three weeks of scheduled retreatment (i.e., beyond Day 43) will be removed from the study and followed for progression and survival. Reassessment of disease status by CT scan and bone scan will be done at time of removal of study if not done within the previous 28 days.

4.5 Duration of Therapy

In the absence of treatment delays due to toxicity(ies), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Life threatening or other unacceptable drug-related toxicity as described in sections 4.3.1 and 4.3.2.6.3,
- Lack of recovery from toxicity after three weeks after re-evaluation of their disease status with bone scan and CT scan,
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Clinicians must exercise their discretion in treating patients with mitoxantrone beyond a cumulative dose of 140mg/m^2. When a patient is discontinued from the study, the reason(s) for discontinuation should be documented. Follow-up should be maintained and reported. When discontinued from treatment, patients will be followed every three months until death. Patients who experienced any drug-related toxic effects will be followed at least every four weeks until all study drug-related toxicities resolve, stabilize, return to baseline, or are deemed irreversible.

5.0 DRUG INFORMATION

5.1 BMS-247550 (ixabepilone)

5.1.1 Investigational Product Identification (adapted from the Investigators Brochure)

BMS-247550 (ixabepilone) is a semi-synthetic analog of the natural product epothilone B, a non-taxane tubulin polymerization agent obtained by fermentation of the myxobacteria *Sporangium cellulosum*. BMS-247550 (ixabepilone) has a molecular formula of $C_{27}H_{42}N_2O_5S$ and its molecular weight is 506.71 grams/mole.

How Supplied: BMS-247550 (ixabepilone) appears as a lyophilized, white to off-white color, whole or fragmented cake in a vial. The drug product is available in three different potencies: 15 mg/vial, 20 mg/vial, and 30 mg/vial.

BMS-247550 (ixabepilone) vial size	Diluent provided	Volume of diluent needed for reconstitution of drug vial	Final concentration	Actual Amount of Drug in Vial**
15 mg	One 8 mL vial	8 mL	2 mg/mL	16 mg
20 mg	Two 5.5 mL vials	11 mL	2 mg/mL	22 mg
30 mg	One 16.5 mL vial	16.5 mL	2 mg/mL	33 mg

***To account for vial/needle/syringe loss, the actual amount of drug in the vial differs from the amount of drug on the product label.*

The Vehicle for Constitution of BMS-247550 (ixabepilone) for injection (diluent) appears clear to slightly hazy and is colorless to pale in color. The diluent is comprised of an ethanol plus polyoxyethylated castor oil (Cremophor® EL) mixture (1:1 by volume).

The drug vial should only be reconstituted with the provided diluent. The diluents are not interchangeable and should only be utilized to reconstitute a particular strength.

5.1.2 Handling and Dispensing of Investigational Product

Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In addition, for IND studies, the study drug must be dispensed only from the institution(s) specified on the FDA Form 1572.

Storage

BMS-247550 (ixabepilone)hg for Injection should be stored refrigerated at 2°C to 8°C (36 to 46°F), and protected from light prior to use.

The Vehicle for Constitution should be stored at 2° to 8°C, or 2° to 25°C, as directed on the product label.

Stability

Shelf life surveillance is ongoing. After initial constitution with the accompanying diluent, the constituted product may be stored in the vial for a **maximum time of 1 hour** at room temperature and room light.. After final dilution in Lactated Ringer™s Injection(LRI) to BMS-247550 (ixabepilone) concentrations between 0.2 and 0.6 mg/mL, the drug product is stable at room temperature and room light for a **maximum of 6 hours**. Please note that BMS-247550 (ixabepilone) concentrations below 0.2 mg/mL are no longer recommended.

Preparation

Prior to constitution of the lyophile, the diluent vial(s) should be kept at room temperature for approximately one hour. (See storage section. If the diluent is labeled to stored in the refrigerator, it must be kept at room temperature for 1 hour prior to mixing.) Inject 8 mL, 11 mL, and 16.5 mL of the diluent into the 15 mg vial, 20 mg vial, and 30 mg vial, respectively. Gently swirl the vial until the lyophile

is completely dissolved. In all cases, this results in a 2mg/mL solution. The vial sizes and the required amount of diluent are summarized in the table above.

This solution must be further diluted with Lactated Ringer's Injection (LRI) to a final BMS-247550 (ixabepilone) concentration ranging from 0.2 mg/mL to 0.6 mg/mL in a non-PVC container before administration to the patient. (Please note: BMS-247550 (ixabepilone) concentrations below 0.2 mg/mL are no longer recommended. Any remaining solution should be discarded according to institutional procedures for cytotoxics.

Note: **15 mg/vial potency**: The label fill for the drug is 15 mg/vial, which is to be constituted to a concentration of **2 mg/mL** with the diluent. To account for vial/needle/syringe (VNS) loss, the actual amount of drug in the vial is **16 mg** (+/- 3%). Hence, the drug should be constituted using **8.0 mL** of the vehicle for constitution (to achieve a BMS-247550 (ixabepilone) concentration of 2 mg/mL).

Note: 20 mg/vial potency: The label fill for the drug is 20 mg/vial which is to be constituted to a concentration of 2 mg/mL with the diluent. To account for vial/needle/syringe (VNS) loss, the actual amount of drug in the vial is 22 mg (+/- 3%). Hence, the drug should be constituted using 11 mL of the vehicle for constitution (to achieve a BMS_247550 concentration of 2 mg/mL).

Note: 30 mg/vial potency: The label fill for the drug is 30 mg/vial which is to be constituted to a concentration of 2 mg/mL with the vehicle. To account for vial/needle/syringe (VNS) loss, the actual amount of drug in the vial is 33 mg (+/- 3%). Hence, the drug should be constituted using 16.5 mL of the vehicle for constitution (to achieve a BMS-247550 (ixabepilone) concentration of 2 mg/mL).

Route of Administration:
BMS-247550 (ixabepilone) must be administered intravenously through an appropriate in-line filter with a microporous membrane of 0.22 to 5.0 microns (See Incompatibilities section for a list of appropriate filters). Lactated Ringer's Injection (LRI) should be used to flush the IV line or extension set at the end of the infusion, if flushing is required.

Incompatibilities
Contact of the diluted product with polyvinyl chloride (PVC) equipment or devices that are plasticized with di- (2-ethylhexyl)pthalate (DEPH) should be avoided to prevent leaching of DHEP into the infusion medium. In order to minimize patient exposure to DHEP, which may be leached from PVC infusion bags or sets, diluted BMS-247550 (ixabepilone) solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets or PVC sets plasticized with TOTM (trioctyl trimellitate). IV sets and components typically used for the administration of paclitaxel have been found to be compatible with infusions of BMS-247550 (ixabepilone).
The following infusions components have been qualified for use with BMS-247550 (ixabepilone):

IV sets containing an in-line 0.22 micron filter

- Baxter Vented Paclitaxel Set (Catalog #2C7553)

- Abbott Primary IV Plumset (Catalog #11947)

IV sets not containing an in-line 0.22 micron filter (need to add one of the filters below)

- McGaw AccuPro Pump Nitroglycerine IV Set (Catalog #V8333)
- Clintec IV Fat Emulsion Set (Catalog #2C1105)

Filter extension set (to be used with IV sets not containing an in-line filter)

- Braun Filter Extension Set with 5 Micron Filter (Catalog #FE-5010Y)

Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

5.1.3 Resupply Requests

BMS-247550 (ixabepilone) may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that BMS-247550 (ixabepilone) be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Cirriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

BMS-247550 (ixabepilone) may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9000 Rockville Pike, EPN Room 7149, Bethesda, MD 20892-7422 of faxing it to (301) 480-4612. For questions call (301) 496-5725

5.1.4 Investigational Product Records at Investigational Site(s)

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.
- Amount destroyed at study site, if applicable.
- The standard NCI Drug Accountability Record Form must be utilized.

5.1.5 Return of Investigational Product

Upon completion or termination of the study, all unused investigational product that cannot be transferred to an open BMS247550 (ixabepilone) protocol must be returned to the NCI, if not authorized by the NCI to be destroyed at the site. Empty vials should be discarded at the investigative site according to appropriate drug disposal procedures.

All drug returns to the NCI must be accompanied by the appropriate documentation and be clearly identified by protocol number and study site number on the outermost shipping container. Details regarding packing supplies for return, as well as the address to which such supplies should be sent, will be provided to the study site.

5.1.6 Destruction of Investigational Product

If BMS-247550 (ixabepilone) is destroyed at the site, it is the Investigator's responsibility to ensure that:

- Procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures;
- Written authorization for disposal/destruction has been granted by the NCI;
- Arrangements have been made for the disposal; and
- Appropriate records of the disposal have been documented.

5.1.7 BMS-247550 (ixabepilone) Adverse Events

Adverse Events with Possible Relationship to BMS-247550 (CTCAE v3.0 Term) [n=708 patients]			**"Agent Specific Adverse Event List" (ASAEL)**
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**	
ALLERGY/IMMUNOLOGY			
	Allergic reaction/hypersensitivity (including drug fever)		***Allergic reaction/hypersensitivity (including drug fever)***
BLOOD/BONE MARROW			
	Hemoglobin		
	Leukocytes (total WBC)		***Leukocytes (total WBC)***
	Lymphopenia		
	Neutrophils/granulocytes (ANC/AGC)		***Neutrophils/granulocytes (ANC/AGC)***
	Platelets		***Platelets***
CARDIAC ARRHYTHMIA			
	Sinus bradycardia		***Sinus bradycardia***
CARDIAC GENERAL			
	Cardiac ischemia/infarction		
	Cardiac troponin T (cTnT)		
	Hypotension		***Hypotension***
COAGULATION			
	INR (International normalized ratio of prothrombin time) in patients on Coumadin		***INR (International normalized ratio of prothrombin time) in patients on Coumadin***
CONSTITUTIONAL SYMPTOMS			
Fatigue (asthenia, lethargy, malaise)			***Fatigue (asthenia, lethargy, malaise)***
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)		***Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)***

	Insomnia		***Insomnia***
	Weight loss		
DERMATOLOGY/SKIN			
	Flushing		***Flushing***
Hair loss/alopecia (scalp or body)			***Hair loss/alopecia (scalp or body)***
	Injection site reaction/extravasation changes		
	Nail changes		***Nail changes***
	Pruritus/itching		***Pruritus/itching***
	Rash: dermatitis associated with radiation: Chemoradiation		***Rash: dermatitis associated with radiation: Chemoradiation***
	Rash/desquamation		***Rash/desquamation***
	Rash: hand-foot skin reaction		
GASTROINTESTINAL			
Anorexia			***Anorexia***
	Constipation		***Constipation***
	Dehydration		***Dehydration***
Diarrhea			***Diarrhea***
	Dysphagia (difficulty swallowing)		
	Esophagitis		
	Heartburn/dyspepsia		
Mucositis/stomatitis (functional/ symptomatic) - Select			***Mucositis/stomatitis (functional/symptomatic) - Select***
Nausea			***Nausea***
	Taste alteration (dysgeusia)		***Taste alteration (dysgeusia)***
	Ulcer, GI: duodenum		
Vomiting			***Vomiting***
HEMORRHAGE/BLEEDING			
	Hemorrhage, GI: rectum		
HEPATOBILIARY/PANCREAS			
	Liver dysfunction/failure (clinical)		
INFECTION			
	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C)		***Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C)***
	Infection with Grade 3 or 4 neutrophils - Select		***Infection with Grade 3 or 4 neutrophils - Select***
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select		***Infection with normal ANC or Grade 1 or 2 neutrophils - Select***
	Infection with unknown ANC - Select		***Infection with unknown ANC - Select***
LYMPHATICS			
	Edema: head and neck		
	Edema: limb		
	Edema: trunk/genital		
	Edema: viscera		
METABOLIC/LABORATORY			
	Creatinine		
MUSCULOSKELETAL/SOFT TISSUE			
	Muscle weakness - whole body/generalized		***Muscle weakness - whole body/generalized***
NEUROLOGY			

	Ataxia (incoordination)		
	Dizziness		***Dizziness***
	Neuropathy: motor		***Neuropathy: motor***
Neuropathy: sensory			***Neuropathy: sensory***
	Speech impairment (e.g., dysphasia or aphasia)		***Speech impairment (e.g., dysphasia or aphasia)***
	Syncope (fainting)		***Syncope (fainting)***
OCULAR/VISUAL			
	Watery eye (epiphora, tearing)		***Watery eye (epiphora, tearing)***
PAIN			
	Pain - abdomen NOS		
	Pain - bone		
	Pain - extremity-limb		***Pain - extremity-limb***
	Pain - head/headache		
Pain - joint			***Pain - joint***
Pain - muscle			***Pain - muscle***
	Pain - neuralgia/peripheral nerve		***Pain - neuralgia/peripheral nerve***
	Pain - tumor pain		***Pain - tumor pain***
PULMONARY/UPPER RESPIRATORY			
	Cough		***Cough***
	Dyspnea (shortness of breath)		***Dyspnea (shortness of breath)***
	Hiccoughs (hiccups, singultus)		***Hiccoughs (hiccups, singultus)***
	Hypoxia		***Hypoxia***
	Pneumonitis/pulmonary infiltrates		***Pneumonitis/pulmonary infiltrates***
RENAL/GENITOURINARY			
	Urinary retention (including neurogenic bladder)		***Urinary retention (including neurogenic bladder)***
VASCULAR			
		Acute vascular leak syndrome	***Acute vascular leak syndrome***

Also reported on BMS-247550 trials but with the relationship to BMS-247550 still undetermined:

Allergy/Immunology – rhinitis
Auditory/Ear – hearing loss
Cardiac Arrhythmia – atrial fibrillation; palpitations; sinus tachycardia; supraventricular arrhythmia; vasovagal episode
Cardiac General – hypertension; left ventricular cardiac function; pericardial effusion
Coagulation – DIC; PTT
Constitutional Symptoms – rigors/chills; sweating
Dermatology/Skin – dry skin; pigmentation changes; urticaria
Endocrine – hot flashes
Gastrointestinal – colitis; dry mouth; flatulence; gastritis; GI perforation; paralytic ileus
Hemorrhage/Bleeding – CNS hemorrhage; epistaxis; hematemesis; hemoptysis
Infection – opportunistic infection
Metabolic/Laboratory – acidosis; alkaline phosphatase; ALT; amylase; AST; CPK; hyperbilirubinemia; hypercalcemia; hyperglycemia; hyperkalemia; hypermagnesemia; hypertriglyceridemia; hypoalbuminemia; hypocalcemia; hypoglycemia; hypokalemia; hypomagnesemia; hyponatremia; hypophosphatemia
Neurology – agitation; anxiety; CNS ischemia; confusion; depressed level of consciousness; depression; encephalopathy; peripheral autonomic neuropathy; seizure
Ocular/Visual – blurred vision; conjunctivitis; double vision; dry eye; papilledema
Pain – back pain; chest pain; dysuria; earache; pelvic pain; pleural pain
Pulmonary/Upper Respiratory – pleural effusion; pneumothorax; respiratory failure; voice changes

Renal/Genitourinary – renal failure; urinary frequency; urinary incontinence
Sexual/Reproductive Function – irregular menses; libido; vaginitis
Vascular – thrombosis/embolism; vascular access complication

Note: BMS-247550 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.1.8 Potential Drug Interactions: *In vitro* studies indicate that the main route of oxidative metabolism of BMS247550 (ixabepilone) is via cytochrome P450 CYP3A4. A study of the effect of the CYP3A4 inhibitor ketoconazole on the safety tolerability, and pharmacokinetics of BMS-247550 (ixabepilone) is ongoing. An increase in exposure to BMS-247550 (ixabepilone) (mean Cmax and AUC increased by 21% and 90%, respectively based on preliminary results in 7 patients) was observed in patients when a single dose of BMS-247550 (ixabepilone) was coadministered with 6 daily doses of 400 mg of ketoconazole, a strong CYP3A4 inhibitor.

It is not recommended to use BMS-247550 (ixabepilone) concomitantly with the below listed moderate to significant inhibitors of CYP3A4

Inhibitors of CYP3A4:
Antibiotics: clarithromycin, erythromycin, troleandomycin
Anti-HIV agents: delavirdine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir
Antifungals: itraconazole, ketoconazole, fluconazole (doses >200 mg/day)
Antidepressants: nefazodone, fluovoxamine
Calcium channel blockers: verapamil, diltiazem
Miscellaneous: amiodarone

In vitro, BMS-247550's weak inhibition of human CYP3A4 suggests that it may have a minimal potential to alter the metabolic clearance of drugs that are metabolized by CYP3A4. BMS-247550 (ixabepilone) had no effect on human CYP1A2, CYP2C9, CYP2C19, and CYP2D6.

5.2 Mitoxantrone hydrochloride:(16)

Human Toxicology: Dose limiting toxicities of mitoxantrone are myelosuppression and cardiotoxicity. Leukopenia and thrombocytopenia were maximal by day 9 and resolved by day 9-21. Other toxicities seen occasionally include stomatitis, nausea and vomiting, phlebitis, mild elevations in SGOT, alopecia, dyspnea, urticaria, rash, hypotension, arrhythmias, and chest pain. Mitoxantrone may impart a blue-green color to the urine for 24 hours after administration; patients should be advised to expect this during therapy. Bluish discoloration of the sclera may also occur. Cardiotoxicity may be more common in patients previously treated with anthracyclines or mediastinal radiotherapy, or in patients with pre-existing cardiac disease. Mitoxantrone may cause fetal anomalies, and is mutagenic in bacterial systems. Extravasation may cause local tissue necrosis.

Pharmacology: Mitoxantrone hydrochloride is a synthetic antineoplastic anthracenedione for intravenous use. The molecular formula is C 22 H 28 N 4 O 6 ·2HCl and the molecular weight is 517.41. It is supplied as a concentrate that must be diluted prior to injection. The concentrate is a sterile, nonpyrogenic, dark blue aqueous solution containing mitoxantrone hydrochloride

equivalent to 2 mg/mL mitoxantrone free base, with sodium chloride (0.80% w/v), sodium acetate (0.005% w/v), and acetic acid (0.046% w/v) as inactive ingredients. The solution has a pH of 3.0 to 4.5 and contains 0.14 mEq of sodium per mL. The product does not contain preservatives. The chemical name is 1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl) amino]ethyl]amino]-9,10-anthracenedione dihydrochloride. Pharmacologic studies in dogs have shown that mitoxantrone clears rapidly from the plasma. Clinical pharmacologic studies in humans showed a rapid distribution half-life (on the order of 8 minutes), and an elimination half-life of two hours. Most of the drug is excreted via the biliary system, with about 10% excreted in the urine. Mitoxantrone has been found to be tolerable when administered on a three week schedule.

Formulation: Mitoxantrone is supplied as a dark blue sterile concentrated solution containing mitoxantrone hydrochloride equivalent to 2mg/ml mitoxantrone free base. The concentrate is supplied in 10, 12.5, and 15mL vials and must be diluted prior to injection.

Administration: The dose of Mitoxantrone should be diluted in a solution of at least 50 mL of D5W or NS. Mitoxantrone should not be mixed in the same infusion as heparin since a precipitate may form. Because specific compatibility data are not available, it is recommended that mitoxantrone not be mixed in the same infusion with other drugs. The diluted solution should be introduced slowly into the tubing as a freely running intravenous infusion over 30 minutes. DO NOT GIVE IV PUSH.

Mitoxantrone must never be given subcutaneously, intramuscularly, or intra-arterially. Severe local tissue damage may occur if there is extravasation during administration. If extravasation occurs, the administration should be stopped immediately and restarted in another vein. The extravasation site should be carefully monitored for signs of necrosis and/or phlebitis that may require further medical attention. Care should be taken to avoid extravasation at the infusion site and to avoid contact of mitoxantrone with the skin, mucous membranes or eyes. Skin accidentally exposed to mitoxantrone should be rinsed copiously with warm water and if the eyes are involved, standard irrigation techniques should be used immediately. The use of goggles, gloves, and protective gowns is recommended during preparation and administration of the drug.

Storage and stability: Mitoxantrone does not contain any preservatives and is stored at room temperature. Discard any unused drug after eight hours of puncturing the ampule. The expiration date of each ampule is provided on the label. The mitoxantrone solution should be used within 24 hours of preparation.

Safety Precautions: Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

Supplier: Mitoxantrone is commercially available, and commercial sources will be used.

Further information about mitoxantrone can be found in the manufacturer's package insert.

5.3 Prednisone:(17)

Human toxicology: Adverse affects associated with prednisone use are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, worsening of infection (i.e., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo, headache, endocrine abnormalities, ophthalmic changes, and metabolic

changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia, and arthralgia. Phenytoin, phenobarbital, and ephedrine increase metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulosis, fresh intestinal anastamoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Immunization procedures (especially smallpox) should not be undertaken in patients on corticosteroids.

Pharmacology: Glucocorticoids are quickly and completely absorbed from the GI tract.

Formulation: Refer to package insert.

Storage and stability: Prednisone should be stored at room temperature.

Administration: Prednisone is administered orally.

Supplier: Prednisone is commercially available, and commercial sources will be used.

Further information about prednisone can be found in the manufacturer's package insert.

6.0 MEASUREMENT OF RESPONSE

6.1 Measurement of response in patients with measurable disease

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.(14) Changes in only the longest diameter (unidimensional measurement- LD) of the tumor lesions are used in the RECIST criteria.

Note: lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy. All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 30 days before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous

reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

6.1.1 Measurable disease/ Target lesions

All measurable lesions (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as ≥10mm with spiral CT) up to a maximum of 5 lesions per organ and 10 lesions total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and the suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as a reference by which to characterize the objective tumor response.

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (including baseline LD), or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started (including baseline LD)

6.1.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s), and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions, and/or unequivocal progression of existing non-target lesions

Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the study chair.

6.1.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started, including baseline; see table below). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

6.1.4 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum of 12 weeks after study entry.

6.1.5 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Target Lesions	Non-Target Lesions	New Lesions	Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

6.2 Post-treatment PSA Changes

All patients, with or without measurable or non-measurable disease, will be evaluated for PSA decline.(13) Patients with disease that is not measurable will be eligible for this study and will be assessed for response based on changes in PSA and serial bone scans (if appropriate). The baseline serum PSA must be at least 5 ng/mL. Patients who show PSA progression at two cycles may receive a third cycle of chemotherapy prior to determining PSA progression.

a. 50% PSA Decline: PSA decline of at least 50% from baseline confirmed by a second measurement at least 4 weeks later. The reference for these declines should be a PSA measured within 2 weeks prior to starting therapy.

b. PSA Progression: If at least a 50% PSA decline has been achieved, PSA progression occurs when the PSA has increased to 50% above the nadir and the increase in the absolute-value PSA level is at least 5 ng/mL, or back to baseline, whichever is lower,

on at least 2 measurements at least 2 weeks apart. For patients without a PSA decline of this magnitude, or without any decline in PSA, progression will be defined by a 25% increase over baseline or nadir PSA (whichever is lower), and an increase in the absolute-value PSA level by at least 5 ng/mL, on at least 2 measurements, at least 2 weeks apart.

c. PSA Response Duration: The PSA response duration commences on the date of the first 50% decline in PSA. The response duration ends when the PSA value increases by 50% above the nadir, provided that the increase in the absolute-value PSA level is at least 5 ng/mL or back to baseline, whichever is lower.

d. Progressive Disease: Defined by PSA Progression (see section 8.2.b) or the appearance of 1 or more new measurable or non-measurable lesions occurring more than 1 month after the initiation of therapy.

e. Time to PSA Progression: The start of the time to PSA progression is the day treatment is initiated. The end date is the time of PSA progression as defined in section 6.2.b (PSA Progression), above.

6.3 Progressive disease (PD)

Progressive disease will be defined by <u>any one</u> of the following:

1. PSA progression as defined above
2. Appearance of new metastatic lesions outside the bone
3. New metastatic lesions on bone scan
4. Development of an indication for radiotherapy while on treatment
5. Unequivocal progression of non-target lesions

7.0 STATISTICAL CONSIDERATIONS

7.1 Phase I: The primary endpoint of the phase I study is safety. Successive cohorts of patients will be accrued to determine the maximum tolerated dose that results in <33% dose-limiting toxicities with the combination of BMS-247550 (Ixabepilone) and mitoxantrone as chemotherapy for HRPC patients with disease progression after taxane chemotherapy. The MTD of the regimen will be determined using standard phase I methodology. Cohorts of 3 patients will be enrolled at each dose level; if 1 DLT is observed then the cohort will be expanded to 6 patients. If a second DLT is observed, the previous dose level will be considered the MTD. If all observed DLT are due to neuropathy (specific to ixabepilone), then we would consider the previous dose level of BMS-247550 (Ixabepilone) the MTD for that drug, and escalate mitoxantrone as described above to a maximum dose of 12 mg/m^2. At least 6 patients will be treated at the MTD to increase the likelihood that the risk of a DLT is <33%. These 6 patients will be included in the phase II component for response analysis. After the MTD has been defined, the phase II portion of the study will begin to determine the level of activity of this three-drug combination for prostate cancer chemotherapy. Descriptive statistics will be calculated to characterize the disease and previous treatment features as well as the details of protocol therapy. Toxicities will be tabulated by grade for each dose cohort and overall for all patients accrued to the phase I study.

7.2 Phase II: The primary endpoint the phase II study is the proportion responding to treatment with of the combination of BMS-247550 (Ixabepilone) and mitoxantrone with prednisone in HRPC patients who have had prior taxane chemotherapy based upon a PSA decline

of >50%. Patients will be evaluated with CT and bone scans after every 3 cycles. Objective responses of bidimensionally measurable disease, and time to progression will also be evaluated. Treatment of 58 patients at the dose will allow for the detection of a 35% PSA response proportion, compared with a null hypothesis of 20%, with a power of 0.90 and a level of significance of 0.10. Simon's minimax 2-stage design will be employed to carry out an interim analysis for efficacy. If 6 or fewer of 33 patients show >50% PSA declines after 3 cycles, accrual will be discontinued. The probability of early termination if the null hypothesis is true is 50%.(18)

Descriptive statistics will be calculated to characterize the disease and treatment factors for patients accrued to the phase II study. This includes the proportion responding with a 95% confidence interval. A chi square test will be performed to test the primary study hypothesis of efficacy. The observed proportion of patients achieving a PSA decline of at least 50% will be compared with the hypothesized proportion of 20%. The sample size is sufficient to detect a 35% response. The Kaplan-Meier product limit method will be used to estimate the probability of time to progression and duration of response. Toxicities will be tabulated by grade for the phase II study.

7.3 Secondary objectives include the safety and objective response proportion of this regimen. An interim analysis for safety will be carried after 33 patients have completed 3 cycles of treatment at the same time that the interim analysis for efficacy will be conducted. Unacceptable toxicity is defined as any recurrent treatment-related $\geq$ grade 3 non-hematologic toxicity despite 2 dose reductions and any $\geq$ grade 3 toxicity lasting more than 21 days. Fatigue, anemia, alopecia and toxicities related to androgen deprivation therapy. If unacceptable toxicity occurs among more than 15% of the patients, then this treatment will be considered unacceptable. A test of the null hypothesis of acceptable toxicity of 85% will be compared with the alternative hypothesis of 95% (type I error=0.05, power = 0.84). If an interim analysis of 33 patients indicates that 28 or fewer patients have acceptable toxicity, then accrual will be discontinued due to lack of safety. The probability of stopping at the first stage if the null hypothesis is true is 56% and only 2% under the alternative.

8.0 DATA SAFETY MONITORING PLAN FOR A PHASE I-II CTEP INSTITUTIONAL STUDY

8.1 Oversight and Monitoring Plan

The UCSF-CCC Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UCSF-CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data in each cohort
- Quarterly review for progress and safety
- Review of all serious adverse events
- Minimum of a yearly audit

8.2 Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and patient safety at weekly study group or site committee meetings where the results of each patient's treatment are discussed and the discussion is documented in the minutes. The discussion will include for each dose level, the number of patients, significant toxicities as described in the protocol, doses adjustments, and

observed responses. Quarterly summaries will be submitted to the DSMC for review. All grade 3-5 AE's and SAE's will be entered in the CCC Velos eResearch database. The study coordinator will keep a log of subject(s) at each dose level. Dose limiting toxicities will be documented on the log. At the time of dose escalation a written report will be submitted to the DSMC Chair outlining the cohorts dose, grade3-5 AEs and SAE reports, and if any Dose Limiting Toxicity as described in the protocol. The report will be reviewed by the chairman or designee (maximum time 5 working days) and written authorization to proceed or a request for more information will be issued.

8.3 Review and Oversight Requirements

8.3.1 Adverse Event Monitoring

Adverse Events (AEs) will be recorded on the Velos eResearch database all grade 3-5 expected and unexpected AEs will be recorded and updated at each visit.

8.3.2 Serious Adverse Event Reporting

Serious Adverse Event reporting will be in accordance with the UCSF- Committee on Human Research Regulations and Code of Federal Regulation Title 21 Volume 5 Part 312.32 and the Cancer therapy Evaluation Program (CTEP)

UCSF CHR website for guidance in reporting serious adverse events
http://www.research.ucsf.edu/chr/Guide/chrA_AE.asp

FDA website for guidance in reporting serious adverse events
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32

CTEP Adverse Event Reporting requirements:
http://ctep.cancer.gov/reporting/index.html

Serious Adverse events will be reported on the AdEERS form. A copy of the AdEERS report and CHR forms must be sent to CCC- DSMC at Box 1297. The date the SAE was sent to all required reporting agencies will documented on Velos, hard copies of the report will be maintain in the regulatory files.

If the SAE is death and determine to be possible, probably or definitely related to the investigational drug or any research related procedure the event must be reported to the DSMC Chair, or his designee within 24 business hours. The reporting procedure is by personal communication via phone or in person with written documentation of the 1:1 communication via e-mail with a copy of the e-mail to DSMC Administrator and DSMC Coordinator.

If any of the above action occurs in multiple-institutional clinical trial coordinated by the UCSF-CCC, the Study Coordinator will insure that all participating sites are notified.

8.3.3 Review of Adverse Event Rates

If the study has an increase of unexpected or expected Adverse Event grade 3 or 4 above the rate reported in the Investigational brochure or package insert, this will be reported to the DSMC at the time of identifying the increased rate, each quarterly report will indicate if the AE incidence is

within the scope of the investigational brochure or package insert. If at any time the Investigator stops enrollment or stops the study due to safety issues the DSMC Chair and Administrator must be notified within 24 business hours via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

If any of the above action occurs in multiple-institutional clinical trial coordinated by the UCSF-CCC, the Study Coordinator will insure that all participating sites are notified.

8.3.4 Study Progress – Quarterly Review

Principal Investigators are required to submit quarterly study progress reports to determine whether accrual projections are being met, to summarize grade 3 and 4 toxicities (expected and unexpected) and SAE reports, in addition a progress report on recruitment and subjects known responses to the investigational therapy. At this time also end the committee all external DSMB reports and formal audit reports.

These quarterly reports are reviewed at Data Safety Monitoring Committee meetings. These reports are required: February 1, May 1, August 1, and October 1. Failure to submit such reports may result in trial suspension.

Data Safety Monitoring Committee Contacts:
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Box 1705

DSMC Administrator: Diane Davies, RN
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9.0 REPORTING OF ADVERSE EVENTS

9.1 Adverse Event Classification and Grading

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event monitoring and reporting. The CTCAE v3.0 can be downloaded from the CTEP homepage (available at http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

9.2 Expedited Adverse Event Reporting

This is a clinical trial using an investigational agent (Ixabepilone) in combination with two commercial agents (Mitoxantrone and Prednisone). The combination of an investigational with a commercial agent under a CTEP IND is considered an investigational treatment. Expedited AE

reporting for this study must **only** use AdEERS (Adverse Event Expedited Reporting System) following the CTEP, NCI Guidelines. These guidelines and access to the AdEERS program can be found via the CTEP website at http://ctep.cancer.gov/reporting/adeers.html.

In the rare occurrence when Internet connectivity is lost

- AE report may be submitted using CTEP's Adverse Event Expedited Report Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159.
- A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, **only** when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site.

Phase 1 Trials AdEERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
AdEERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Phase 2 and 3 Trials AdEERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
AdEERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: Death occurring after last dose of an agent under CTEP IND must be submitted via AdEERS within timelines outlined in the tables above.

- Any death occurring within 30 days of the last dose regardless of attribution to an agent under CTEP IND (24-hour notification is not required for death clearly related to progressive disease.)
- Any death occurring greater than 30 days after the last dose with an attribution of possible, probably, or definite to an agent under CTEP IND.

Expedited AE reporting timelines defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.

- "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

10.0 CTEP DATA REPORTING AND CLINICAL TRIALS AGREEMENT

10.1 Data Reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site http://ctep.cancer.gov/reporting/cdus.html

The coordinating site is responsible for all CDUS submissions. CDUS submissions from UCSF CCC are conducted through a data transfer from Velos; therefore it is imperative that each participating site ensure that all data for enrolled patients is entered into Velos eResearch at the time of each CDUS submission.

Data collected during this study will be entered into a secure database (Velos eResearch). The coordinating center at MSKCC will be responsible for initial study configuration and setup in Velos eResearch (including CRF setup) and any future changes. The coordinating center will also assist the lead center with data management.

10.2 Clinical Trials Agreement (CTA)

The study agent BMS-247550 used in this protocol is provided to the NCI under a CTA between Bristol-Myers Squibb [hereinafter referred to as Collaborator(s)] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to the Collaborator" terms of award modifications, apply to the use of BMS-247550 in this study:

1. BMS-247550 may not be used for any purpose outside the scope of this protocol, nor can BMS-247550 be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for BMS-247550 are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators

2. For a clinical protocol where there is an investigational agent used in combination with (an) other investigational agent(s), each the subject of different CTAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for the development, regulatory approval, and commercialization of its own investigational agent.

3. Clinical Trial Data and Results and Raw Data developed under a CTA will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator(s) intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator(s) for courtesy review following

submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Room 7111
Bethesda, MD 20892
Fax: 301-402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator(s)

11.0 CTEP MULTICENTER GUIDELINES

11.1 Central Registration

See Section 3.4

11.2 Data Collection

The submission schedule is detailed below. Forms should be submitted via the Velos eResearch database website. Each site has their own link to Velos eResearch. If a site does not have access to Velos eResearch, then all forms should be faxed to 415-353-9566. Please call 415-885-7329 when sending a submission so that the Clinical Research Coordinator knows to expect the fax.

Data Submission Schedule

Form	**Submission Schedule**
Enrollment Eligibility Checklist	At registration for treatment assignment
On-Study Form Prostate Cancer Clinical History Radiographic Staging Specimen Submission	within 2 weeks of registration
Patient Update Adverse Events Drug Accountability	every cycle
Radiographic Staging Specimen Submission	every 3 cycles
Off-Treatment Patient Update Adverse Events Drug Accountability Radiographic Staging Specimen Submission	At time of removal from protocol
Death Notification	At time of death (during or 30 days after last dose)

Supplemental forms – progress note and patient study flowsheet will be provided and may be requested by UCSF research staff.

11.3 Adverse Event Reporting

When indicated, each site will submit their own adverse events using AdEERS (see Section 9.0). When submitting the AdEERS report, the Clinical Research Coordinator must carbon copy (cc) the UCSF Clinical Research Coordinator to inform him/her that an AdEERS report has been submitted. The UCSF Clinical Research Coordinator must disseminate this information to all other sites. All sites must review and process the AdEERS report and follow institutional standards for submitting a safety report.

11.4 Quality Assurance

Weekly registration reports will be generated for each affiliate site to monitor patient accruals and completeness of registration data. Data queries will be generated for the affiliates when there are questions or incomplete data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Each affiliate will receive these reports periodically, they will be expected to review and respond to the data queries as appropriate.

There will be random-sample data quality and protocol compliance audits at the Coordinating Center (UCSF), conducted by the study team, at a minimum of one time per year, more frequently if indicated. The Coordinating Center (UCSF) will be responsible for conducting on site audits at the affiliate sites. The audits will represent the standard NCI data accuracy (CRF/source) and protocol compliance reviews. The results will be reported back to UCSF and the affiliates.

APPENDIX 1: ECOG Performance Status Scale

DESCRIPTION	SCALE
Normal Activity	0
Symptoms of disease, able to carry out activities of daily living	1
Out of bed >50% of time; occasionally needs help	2
In bed >50% of time; needs nursing care	3
Bedridden; may need hospitalization	4

APPENDIX 2 Preliminary AE's observed on NCI 6046

Out of 70 patients enrolled on NCI 6046 as of 4/30/05.

	Ixabepilone 2nd-line (n=32)		Ixabepilone 3rd-line (n=23)		MP 2nd-line (n=38)		MP 3rd-line (n=10)	
Adverse Event	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade4**	**Grade 3**	**Grade 4**
Abnormal PT/PTT	1 (3%)		2 (9%)		3 (3%)			
Allergic hypersensitivity reaction		1 (3%)	1 (4%)					
Anorexia	1 (3%)							
Constipation					1 (3%)			
Chest pain	1 (3%)							
Elevated creatinine		1 (3%)						
Dehydration			1 (4%)		1 (3%)			
Depression	1 (3%)							
Dizziness/lightheadedness	1 (3%)				1 (3%)			
Fatigue			1 (4%)					
Hypercalcemia		1 (3%)						
Hyperuricemia		1 (3%)						
Hypophosphatemia			1 (4%)					
Hypotension			1 (4%)		1 (3%)			
Infection with neutropenia	1 (3%)		1 (4%)					
Infection without neutropenia			1 (4%)					
Muscle weakness not due to neuropathy	1 (3%)		1 (4%)		1 (3%)			
Nausea							1 (10%)	
Stomatitis	1 (3%)							
Urinary retention	3 (9%)							
Vomiting							1 (10%)	

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University of California, San Francisco and the Department of Veterans Affairs

Consent to Participate in a Research Study

Study Title: 055513: Phase I/II Trial of Epothilone Analog BMS-247550 (Ixabepilone), Mitoxantrone, and Prednisone in Hormone Refractory Prostate Cancer Patients Previously Treated with Chemotherapy

This is a clinical trial, a type of research study. Your study doctor, Dr. Jonathan Rosenberg, or one of his associates at the University of California San Francisco Comprehensive Cancer Center, or Dr. Patricia Cornett, or one of her associates, at the San Francisco Veterans Affairs Medical Center, will explain the clinical trial to you.

Clinical trials only include people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to participate in this study because you have advanced prostate cancer, which has failed to respond, or stopped responding to first-line chemotherapy including paclitaxel or docetaxel.

Why is this study being done?

There are two parts to this study. The first part, called Phase I, is to determine the highest doses of BMS-247550 (ixabepilone) combined with mitoxantrone/prednisone that does not cause bad side effects. Once these doses have been established, Phase II of the study will test to see how effective this combination of drugs is in treating hormone refractory prostate cancer. Additional data will be collected to see how safe these drugs are when used in combination. The BMS-247550 (ixabepilone) is an experimental drug and will be provided free of charge by the Cancer Therapy Evaluation Program (CTEP), a division of the National Cancer Institute.

How many people will take part in the study?

Up to 36 people will take part in the Phase I portion of this study and an additional 58 people will be treated in the Phase II portion therefore a total of up to 94 patients overall will take part in this study.

What will happen if I take part in this research study?

If you agree to participate in this study the following events will occur:

Before treatment starts

Within 42 days of beginning treatment, you will have a **MUGA** or **echocardiogram**.

- A **MUGA scan** is a special test that determines how well you heart squeezes blood. For this test, you will have a contrast material injected into your vein. You will lie on a table and a special camera will take pictures of your heart. This procedure takes about 45-60 minutes.
- An **echocardiogram** is an ultrasound of your heart that also determines how well you heart squeezes blood. For this test, a probe is placed on your chest over your heart and the movements are recorded. This test is non-invasive (requires no needles or punctures) and takes 45 minutes. Either a MUGA scan or an echocardiogram will be done to determine your heart function prior to any therapy.

- Within 28 days of beginning treatment you will have a **CT scan** (or **MRI**) of the chest, abdomen and pelvis as well as a **bone scan** to record the size and location of your tumor(s).
  - A **CT scan** is a series of X-ray tests and will look at your chest, abdomen and pelvis. You may have a contrast material injected into a vein in your arm. This material may make you feel warm and tingly for a few seconds. You will lie flat on a table that will move you into the CT scan machine. You will be asked not to move and may be asked to hold your breath for a few seconds periodically. The CT scans take approximately 1 1/2 hours.
  - If you receive an **MRI** instead of a CT scan, you will lie down on a narrow bed which will then be placed in a tunnel which is 6 feet long by 2 feet wide. Your participation may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked not to swallow for a while, which can be uncomfortable. You may feel warm during a MRI. Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which could in the process possibly harm you. Precautions have been taken to prevent such an event; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI. MRI scans take about one hour.
  - A **bone scan** is a series of pictures of your bones. This picture may alert your doctors to any possibility of spread of cancer to your bones. A small amount of radioactive substance will be injected into your vein. Three hours later, you will be asked to lie under a machine which will take the pictures. The total time for a bone scan is approxiamately 4 hours.

  The CT scan (or MRI) and bone scan will be repeated every 9 weeks if positive at pre-treatment or if clinically indicated. The CT scan and bone scan will also be repeated when you come off study treatment if you have not had them done within the previous 28 days.
- Within 14 days of beginning treatment you will have a **complete history and physical examination**, including height, weight and a baseline evaluation of symptoms, pain and medications. Your doctor will also thoroughly **review the list of medications** you are

currently taking. Certain medications are known to cause increased levels of BMS-247550 in the body when taken together. It is not recommended that you take any of these medications while also receiving BMS-247550. You will also have about 3 teaspoons of **blood drawn** for blood cell counts, blood chemistries, PSA and testosterone levels.

After treatment begins

The first group of patients to enroll will be in the Phase I portion of the study. The first patients to enroll will receive the lowest doses of mitoxantrone and BMS-247550 (ixabepilone). If no bad side effects are observed, the next group of patients will receive higher doses until the highest doses of mitoxantrone and BMS-247550 (ixabepilone) that do not cause bad side effects has been found or the highest doses that the researchers plan to study has been reached. Once the safest doses of mitoxantrone and BMS-247550 (ixabepilone) have been determined, the second group of patients to enter the study will be treated at those doses. Patients in the Phase I portion of the study will continue treatment at the doses of mitoxantrone and BMS-247550 (ixabepilone) to which they were assigned unless that dose has been determined to be unsafe. Patients treated on the phase I study who remain on therapy after the determination of the dose for the phase II may have their dose escalated to the phase II dose after discussion with their treating physician. All patients will take the same dose of prednisone, 5 mg twice a day and you will be given a daily diary to keep track of how often you take your prednisone.

You will receive treatment in cycles. One cycle lasts 21 days. You will also take **prednisone** 5 mg by mouth twice a day every day while you are receiving treatment. At the end of your treatment, you doctor will advise you how to slowly discontinue taking prednisone.

First day of every cycle (Day 1)

- You will be seen by your doctor for a **physical exam** (30 minutes) and **blood samples** will be drawn (about 3 teaspoons) for blood cell counts and chemistries.
- You will then receive **mitoxantrone** in the outpatient infusion center. An intravenous catheter (IV) is placed in a vein in your arm and you will then receive a thirty minute-infusion of mitoxantrone. You will receive mitoxantrone on Day 1 only of each cycle.
- Following your infusion of mitoxantrone, you will receive an infusion of **BMS-247550 (ixabepilone).** Before the infusion of BMS-247550 (ixabepilone), you will receive medication through your vein to prevent an allergic reaction. You will then receive a three-hour infusion of BMS-247550 (ixabepilone) through the same IV. During the first hour of BMS-247550 (ixabepilone) infusion, your **blood pressure and heart rate** will be checked every 15 minutes by a nurse.

Day 8 and 15 (plus or minus one day) of each cycle

- You will have **blood samples** drawn (about one teaspoon) for blood cell counts.

Every three cycles (every nine weeks)

- You will have a repeat **MUGA or echocardiogram**. You will also have repeat **CT or MRI** scans of the chest, abdomen and pelvis and a repeat **bone scan** if these tests showed any cancer during baseline testing.

How long will I be in the study?

You will continue receiving treatment indefinitely for as long as the treatment is working or until one of the following events occurs:

- Your cancer gets worse
- You develop another illness that prevents further administration of study treatment
- The side effects are too severe
- You do not recover from side effects after a three-week delay in treatment
- You decide to withdraw from the study
- Your study doctor feels your treatment should be discontinued

If you come off treatment for any reason, you will come to the clinic for a follow-up visit. At this time you will have a physical examination, blood tests (about 2 teaspoons) for blood cell counts and chemistries (if not already done within the previous 14 days), repeat CT or MRI scans and repeat bone scan (if not already done within the previous 28 days). After your off-study visit, a member of the study team will check on the status of your health every three months.

You will be informed of any new findings developed during the course of this research study, which may affect your willingness to continue to participate in the study.

Can I stop being in the study?

You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely. It is important that you tell the study doctor if you are thinking about stopping so that any risks from mitoxantrone, prednisone and BMS-247550 (ixabepilone) can be evaluated by your doctor. Another reason to tell your doctor you are thinking about stopping is to discuss what follow-up care and testing could be most helpful to you. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part on the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen the side effects. Many side effects go away soon after you stop taking mitoxantrone, prednisone and BMS-247550 (ixabepilone). In some cases side effects can be serious, long-lasting, or may never go away. Since different groups of patients will be getting different doses of mitoxantrone and BMS-247550 (ixabepilone), the risks may be different. Patients who receive the initial, lower doses may be at risk for less of an effect from the drug while patients who receive a higher dose may be at risk for more severe side effects. You can ask your doctor what dose level of study drugs you will be given. It is very important that you talk to your study doctor about any side effects you experience while taking part in this study.

Treatment:

Likely

- Decrease in blood cell counts including white blood cells (which could make you prone to infection), red blood cells (which could cause you to feel tired and short of breath), and platelets (which could cause bruising or bleeding)
- Increases in blood sugar levels, which may cause increased thirst, urination, and fatigue
- Digestive changes including change in appetite, diarrhea, nausea, and vomiting
- Muscle/joint aches
- Numbness and/or tingling in the hands and/or feet
- Fatigue
- Hair loss
- Mouth sores

Less Likely

- Serious infection with or without low white blood cell count
- Elevated liver enzymes in blood which could indicate liver damage
- Elevated blood creatinine, which could indicate kidney damage
- Abnormal mineral content of the blood
- Changes in tests that measure blood thinning for patients taking coumadin
- Allergic reaction
- Fever with or without lowered white blood cell count
- High or low blood pressure
- Abnormal heart function including heart attack, slow heart rate, irregular heart beat, weakening of the heart muscle and/or heart muscle markers
- Swelling of the arms/legs, abdomen, face with accumulation of fluids
- Neurological changes including seizures, confusion, dizziness, insomnia, loss of coordination, or loss of the ability to speak and/or arrange words in an understandable way
- Muscle weakness possibly due to nerve damage
- Pain including headache, bone, tumor, back and/or abdominal pain
- Digestion changes including heartburn/upset stomach, constipation, and dehydration
- Stomach ulcer
- Intestinal bleeding
- Difficulty swallowing possibly due to inflammation of the esophagus
- Changes in the sense of taste
- Changes in body weight (loss or gain)
- Respiratory changes including inflammation of the lungs, reduced oxygen supply to the tissues, cough, shortness of breath, and/or hiccups
- Urinary changes including difficulty urinating and/or urine discoloration
- Skin changes including injection site reaction, difficulty in wound healing, redness in the face, dry skin, itching, rash (including palms and sides of feet), thinning, and/or blue discoloration
- Eye changes including blue discoloration of the eyes, watering, or cataracts
- Changes in the nails

Rare, but serious

- Leaking of blood vessels which could cause fluid retention
- Abnormal function of the adrenal gland, which can cause weakness and fatigue, low blood pressure, nausea, vomiting, diarrhea, irritability and/or restlessness, loss of bone density
- Abnormal changes in personality

Rare, but serious risks associated specifically with cumulative doses of mitoxantrone (may result in hospitalization or death)

- Congestive heart failure (ineffective pumping of the heart leading to an accumulation of fluid in the body)
- Cardiac arrhythmia (irregular heart beat)

Side effects reported by patients but not proven to be caused by study medications

- Respiratory failure
- Fainting episodes
- Convulsions
- Inadequate blood flow to the brain
- Herpes zoster (shingles)
- Increased urinary urgency or frequency
- Blurred vision
- Dry mouth
- Sweating

In addition, you should **never** stop the prednisone suddenly. If you need to stop the prednisone, your doctor will advise you on how to slowly stop the drug (called a "taper"). If you were to stop taking prednisone suddenly, you could become very weak and tired, develop very low blood pressure, very low blood sugar, and abnormalities of the minerals in your bloodstream. While usually not severe, if not treated, these abnormalities are potentially fatal. If you have a serious illness, infection or trauma, it will be necessary to increase your dose of prednisone. Anytime you see a doctor for any reason, you should tell him/her that you are taking prednisone.

Benadryl: The medication diphenhydramine (benadryl) you will receive before your treatment with BMS-247550 to help reduce the side effects and the chances of having allergic reactions may cause dry mouth and drowsiness.

Venipuncture: The risks of blood drawing include bleeding, bruising, infections and, rarely, nerve damage.

Radiation: CT scans, bone scans, and MRIs are commonly used diagnostic procedures. The amount of radiation you will be exposed to is relatively small. These doses of radiation could be potentially harmful, but the risks are so small that they are difficult to measure. If you have had a lot of x-rays already, you should discuss this with the investigator.The risks of the contrast material used for CT scan include allergic reactions, which are rare, and can sometimes be complicated by low blood pressure, asthma, stroke, and organ damage.

Reproductive: The drugs used in this study may have a risk to an unborn baby. Therefore, you should not father a child while on this study, and you and your partner must practice an effective method of birth control while you are participating in this study.

Secondary malignancies: A number of established chemotherapeutic agents have an inherent risk of causing secondary cancers and/or leukemias. Certain agents in use today, not currently known to be associated with this risk, may be shown at a later time to result in the development of these secondary cancers and/or leukemias

Unknown Risks: The drugs and treatments used to kill cancer cells also affect normal cells and can cause side effects. At this time, all the side effects of this treatment are not known.

Are there benefits to taking part on this study?

It is hoped that this treatment could slow down or stop your cancer although there is no proof that this will happen. The potential benefit to you is that the treatment you receive may prove to be more effective than other available treatments. There are no guarantees that you will benefit from taking part in the study, but knowledge may be gained that will benefit others.

What other choices do I have if I do not take part in this study?

If you choose not to participate in this study you have the following options:

- You could receive supportive care intended to make you comfortable, without anti-cancer drugs which may or may not be beneficial.
- You may receive mitoxantrone/prednisone without participating in the study.
- You may choose another kind of treatment such as chemotherapy with drugs like doxorubicin or cyclophosphamide.
- You may choose to have treatment with another investigational drug.

Will my medical information be kept private?

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record may be created because of your participation in this study. Your consent form and some of your research tests results will be included in this record. The information collected during the study will also be stored in a computer at UCSF. The confidentiality of the center computer record is carefully guarded. No individual identities will be used in any reports of publications resulting from this study.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Authorized personnel within the University, including members of the Committee on Human Research (IRB)
- Representatives from the Food and Drug Administration (FDA)
- The National Cancer Institute (NCI)

- Bristol-Myers Squibb, the manufacturer of BMS-247550 (ixabepilone)

What are the costs of taking part in this study?

Mitoxantrone and prednisone are approved by the FDA for the treatment of prostate cancer and the costs for these drugs and their administration will be billed to you or your insurance company in standard fashion. There will be no cost to you for the BMS-247550 (ixabepilone) or its administration, although the cost of other drugs to prevent nausea or allergic reactions will be billed to you or your insurance company in standard fashion. The Division of Cancer Treatment and Diagnostics, NCI, will provide you with BMS-247550 (ixabepilone) free of charge for this study. Every effort will be made to ensure adequate supplies of the BMS-247550 (ixabepilone), free of charge, for all participants. If the drug becomes commercially available for the treatment of prostate cancer, there is a remote possibility that you may be asked to purchase subsequent supplies. Your physician will discuss this with you should the situation arise. The cost of office visits, laboratory tests and scan and x-rays will be billed to you or your insurance company in standard fashion. Every effort will be made to obtain authorization from your insurance company for all treatments, tests, and doctors office appointments. Insurance companies have sometimes refused to pay for the costs of standard treatment for patients on research studies, in which case you will be responsible for all costs. You should check with the doctors and/or financial counselor if you have questions regarding the costs of treatment and your eligibility for payment programs.

Will I be paid for taking part in this study?

You will not be reimbursed or paid for participating in this study. If new cancer therapies or products are developed from this research, there will be no financial reimbursement to you.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. Jonathan Rosenberg or one of his associates, if you feel you have been injured because of taking part in this study. You can tell your doctor in person or call him/her at 415-353-7171.

If you are injured as a result of being in this study, treatment will be available. If you are eligible for veteran's benefits, the costs of such treatment will be covered by the Department of Veterans Affairs. If not, the costs of such treatment may be covered by the Department of Veterans Affairs or the University of California, depending on a number of factors. The Department of Veterans Affairs and the University do not normally provide any other form of compensation for injury. For further information about this, you may call the V.A. District Counsel at (415) 750-2288 or the office of the UCSF Committee on Human Research at (415) 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and

you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from this institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

The doctor who signed below has discussed this treatment with you and you have been given the opportunity to ask questions. If you have any further questions regarding this treatment or you experience a research-related injury, you should contact Dr. Rosenberg at (415) 353-7171. For questions related to patients' rights and protection, you may contact the Committee on Human Research, which is concerned with the protection of volunteers in research projects. You may reach the committee office between 8:00 am and 5:00 pm, Monday – Friday, by calling (415) 476-1814 or by writing: Committee on Human Research, Box 0962, University of California, San Francisco, CA 94143.

Optional Research

This section of the informed consent is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to.

In addition, as part of a research study, you will be asked if you are willing to provide additional blood and urine samples that will be stored and may be used now or in the future for research purposes. Collection of this blood and urine is not required for routine diagnosis or treatment. These blood and urine samples will receive a code number for identification. Your name and other personal identifying information will be kept in a separate secured file. These blood and urine samples may be used to learn more about how prostate cancer or other diseases develop and/or may result in new products, tests or discoveries. In some instances, these may have potential commercial value. You will not receive any payment or financial benefit from any products, tests or discoveries resulting from future research.

If you agree to give additional specimens, approximately 4 teaspoons of blood and a urine specimen will be collected before you start receiving study treatment and every three cycles thereafter. This additional blood and urine sample will also be collected at the time you discontinue treatment. The additional blood samples will be collected at the same time as your routine lab work so additional needlesticks will not be required. You can decide to stop giving these additional blood and urine samples at any time during the study.

As part of the extra blood and urine samples, information from your medical chart will be collected periodically by the researchers for purposes of the study. None of the findings from these studies of your blood or urine will be recorded in your medical chart.

There will no additional charge for these tests, and you will not receive any payment or financial benefit from any products, tests or discoveries. You may also be asked in the future if you are willing to be in additional research studies. You will not be told the results of any future research. Participation in this extra research is voluntary, and if you choose not to allow the extra blood and urine samples to be collected for research, it will in no way affect your care or participation in the main study. You may at any time contact the researchers and ask that your samples be withdrawn from research use, and any identifiable samples still in their possession will be destroyed. These additional research samples will be kept for an indefinite period of time. You can indicate whether you are willing to allow this extra research by initialing one of the lines below.

_____ **Initials** I **do** allow extra blood and urine samples to be collected and used for additional research purposes as described above.

_____ **Initials** I **do not** allow extra blood and urine samples to be collected and used for additional research purposes as described above.

Consent

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation or disclosure of health information about you.

Participation in research is voluntary. You have the right to decline to participate or withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate, you should sign below.

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Signature of Patient Date

---------- ----------
Signature of Physician Obtaining Consent Date

University of California
San Francisco

UCSF

Urologic Oncology

00 Divisadero Street, 3rd floor
n Francisco, CA 94143-1711
one: 415/353-7171
c: 415/353-7093

July 31, 2006

Mr. Joseph S. Little
Contracting Officer
USA MED RESEARCH
Grants Administration Section
820 Chandler Street, FT. Detrick, MD 21702-5014

RE: Department of Defense Development Award W81XWH-05-1-0403
PI: Jonathan Rosenberg, MD

Dear Mr. Little:

I have been granted a DOD Development Award effective July 1, 2005. The grant provided me with the necessary resources to develop a clinical study in the area of prostate cancer. One of the requirements of the award was that at the end of the grant period, June 30, 2006 I would apply for funding to other research agencies to conduct the clinical trial.

This letter is to certify that I am submitting a grant proposal via the R21 mechanism on August 9th 2006 to the National Cancer Institute entitled "Combination chemotherapy for taxane-refractory hormone refractory prostate cancer" for "NCI 7347: Phase I/II trial of Epothilone Analog BMS-247550 (Ixabepilone), Mitoxantrone, and Prednisone in Hormone Refractory Prostate Cancer Patients Previously Treated with Chemotherapy" to fulfill the terms of my DOD grant.

Sincerely yours,

Jonathan Rosenberg, MD
Principal Investigator

I concur,

Joan Kaiser
UCSF Contracts & Grants Officer

NCI CCC®
Comprehensive Cancer
nter Designated by the
ational Cancer Institute